

On the Salts of Tautomeric
Compounds: The Reac-
tions of Urazole Salts
with Alkyl Halides

DISSERTATION.

SUBMITTED TO THE BOARD OF UNIVERSITY STUDIES OF
THE JOHNS HOPKINS UNIVERSITY IN CON-
FORMITY WITH THE REQUIREMENTS
FOR THE DEGREE OF DOC-
TOR OF PHILOSOPHY.

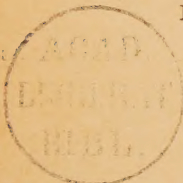
BY
ROGER FREDERIC BRUNEL

EASTON, PA.:
ESCHENBACH PRINTING COMPANY
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On the Salts of Tautomeric Compounds: Reactions of Urazole Salts with Alkyl Halides.

INTRODUCTION.

This work¹ was undertaken to secure some *quantitative* data on tautomerism. Up to that time practically nothing but qualitative work had been done, with the result that especially Nef, Wheeler, Michael, Comstock, Knorr, and Wislicenus had developed theories to account for the interesting phenomena of such tautomeric compounds as quinazolines, amides, acetacetic ester, cyanides, cyanates, pyrazolones, uric acid derivatives, pyrimidines, rosanilines, phenolphthaleins, fluoresceins, etc. All of these theories had much to recommend them, and each one harmonized with most of the qualitative facts known at that time. It was perfectly clear, however, that since qualitative work by these brilliant colleagues for thirty years had not led to any one theory satisfactory to all chemists, further progress in tautomerism should be connected with an accurate *quantitative* investigation of the phenomena, a problem that would occupy a number of chemists for years even if they worked with but one class of substances.

Success in work on a problem depends as much upon the fortunate choice of substances and methods with which to secure *accurate experimental data* as upon the choice of really important points of attack, the solution of which will give us a deep insight into the complexity of the phenomena concerned. Professor Acree and others have since 1896 been investigating the tautomeric phenomena of such amides as triazoles, urazoles, quinazolines, anilides, hydrazides, etc.,

¹ My researches were carried out in 1904-6, and this dissertation is an abstract of my work as presented in 1906. The subject has since been investigated further but the essential conclusions derived from my work at that time remain unchanged to-day. See also Am. Chem. J., **27**, 118; **31**, 185; **32**, 606; **37**, 71, 361; **38**, 1; **39**, 124, 226; **43**, 358. Ber. d. chem. Ges., **33**, 1520; **35**, 553; **36**, 3139; **37**, 184, 618; **41**, 3199. Science, **30**, 617 (1909).

partly with the view of learning what class of substances would ultimately best lend themselves to the accurate study of the problem, and it seemed to me that the urazoles were of all these the ones best adapted to this end. It was all the more desirable to use urazoles and thiourazoles because they are cyclic derivatives of amides and thioamides, which had been the subject of so many beautiful investigations and speculations by Comstock, Wheeler, Nef, Michael, and others. I preferred to use the urazoles, especially 1-phenylurazole and its alkyl derivatives, for the following reasons: (1) This preliminary work had shown that the urazoles are fairly strong acids whose affinity constants can be measured, and which form stable salts not readily hydrolyzed or alcoholized and whose ionization constants in water, alcohol, etc., can therefore be readily measured; (2) I had shown by conductivity methods that these urazoles and their salts do not undergo *slow* tautomeric changes;¹ (3) the urazoles, and especially their salts, react readily at ordinary temperature with alkyl halides, acid chlorides, etc., and yield mixtures of *N*-alkyl (acyl) and *O*-alkyl (acyl) derivatives; (4) the derivatives obtained by alkylation, acylation, etc., seemed to be stable substances which could possibly be estimated quantitatively.

All of these properties of the urazoles seemed to make it possible to obtain, by means of them, some of the factors

¹ In April, May and June, 1905, I carried out a large number of conductivity measurements with 1-phenyl-, 1-phenyl-2-methyl-, 1-phenyl-4-methyl-, 1-phenyl-3-thio-, and 1-phenyl-3-thio-4-methylurazole, and their salts, to determine their ionization constants and thus learn how far the ions and the molecular forms of the salts or acids are concerned in the alkylation, acylation, and other reactions. The salts, at dilutions of from 0.02 N to 0.00003 N, were treated with equivalent quantities of solutions of hydrochloric acid and the conductivities measured at different time intervals to ascertain whether there were slow changes of stronger tautomeric acids into weaker tautomeric acids, or *vice versa*. Taking into consideration changes of temperature on dilution, incomplete mixing, etc., the results showed that there were no appreciable variations in conductivity during even the shortest time periods; in other words, that any possible tautomeric changes take place too quickly to be followed by these methods, a conclusion also borne out by the constancy of the ratio *N*-ester : *O*-ester obtained from the salts and alkyl halides. Mr. E. K. Marshall has now, however, liberated some of these acids from their salts in alcohol at 0° and -70° in the presence of diazo alkyls, which react with great rapidity with these urazole acids, and has found that the acid so liberated may yield a ratio *N*-ester : *O*-ester which is different from that given by the acid if it is allowed to attain equilibrium by standing thirty minutes or longer. This work at low temperatures promises to be of great aid in attempts to ascertain whether tautomeric changes take place in some cases in which no such variations can be detected by other methods at present available.

necessary to the solution of my problem. I hoped afterwards to take up the quantitative study of those urazoles whose tautomeric forms and whose salts can be isolated and are found to change into each other slowly, and whose esters also rearrange.¹

In order to secure the quantitative data necessary to the solution of this problem a large number of things must be investigated, among them:

1. What is the structure of the tautomeric acid or salt?² Are these urazoles and their salts amides, —CONH , or imides, —C(OH) = N— , or are they mixtures of two forms, some of which may be stable and others of which may change into each other? How may the constants involved in the equilibrium be affected by change in temperature, solvents, light, etc.? Does the equilibrium exist between molecules, or ions, or "residues"?

2. What is the mechanism of the reactions involved when the urazole or its salt, apparently a single substance, yields (a) one or (b) two classes of derivatives? Do the ions, or the molecules, or both, or complex groups, react in specific cases?

3. I have first taken up the study of the formation of the *N*-alkyl and *O*-alkyl (acyl, etc.) derivatives by the action of alkyl (acyl, etc.) halides, sulphates, nitrates, etc., on the urazoles and their salts. The following phases of these reactions were the first to be studied. (a) How does the velocity of formation of the *N*-ester and *O*-ester vary with changes in the alkyl halide, salt, solvent, temperature, illumination, electric or magnetic field, concentration, added salt, etc.? (b) Do *different salts* and the same alkyl halide give the same

¹ This has now been done by Dr. Sidney Nirdlinger and Mr. E. P. Doetsch, (1907–1910) whose results will appear later. These colleagues have been able to show that 1,4-diphenyl-3-oxy-5-thionurazole and 1,4-diphenyl-3-oxy-5-thiolurazole, and their salts, rearrange into each other slowly enough to be studied. Each salt yields its own ester.

² Michael: (Ann. Chem. (Liebig), **363**, 20), divides tautomeric compounds into two classes: *desmotropic*, which change their structure reversibly through the movement of a hydrogen atom; and *merotropic*, which, though stable, yield derivatives of an isomer. I do not believe that we have *clear proof* that there is a single *merotropic* substance known to-day. Instead of begging this question I am trying to see whether those substances are not really *desmotropes which change into each very quickly*. Our urazoles, which, from some reactions, appear to be individuals, react at lower temperatures in other cases like mixtures. The subject needs much further work.

or different ratios of *N*-ester : *O*-ester under the same conditions? (c) Do *different alkyl halides* and the same salt yield the same or different ratios *N*-ester : *O*-ester under the same conditions? (d) Does the ratio *N*-ester : *O*-ester change with a variation in the temperature at which these esters are formed? (e) Does the ratio *N*-ester : *O*-ester change with the solvent in which the reaction takes place? (f) Does the ratio *N*-ester : *O*-ester change with the variation in the concentrations of the substances yielding these esters? (g) Does the ratio *N*-ester : *O*-ester change on the addition of a salt having a common cation with the salt yielding the ester, or upon the addition of other electrolytes or nonelectrolytes? Many other such questions have also suggested themselves.

It may be said now that when the theories of Comstock, Wheeler, Nef, and Michael are applied to our urazoles, the conclusions are not in harmony with the experimentally established facts. At the time these theories were proposed they were fine correlations of the known facts and have served beautifully as guides in the later work; they will be found to apply, without doubt, to many other, perhaps limiting, cases.

I. The Theory of Different Structures for the Potassium and Silver Salts of Tautomeric Compounds.

It has long been known that potassium cyanide with alkyl halides gives nitriles while silver cyanide gives isonitriles. The first attempt to explain this was made on the assumption that potassium cyanide is to be represented by the formula KCN, the silver salt by AgNC. In 1891, Comstock and Wheeler¹ noted a similar behavior on the part of the salts of formanilide and advanced the same theory to explain it. This explanation was, of course, based on the belief that the alkali salts give *only a N-derivative* and the silver salts *only an O-derivative*. Friedländer² obtained similar results with certain oxyquinazoline derivatives, and Wheeler³ later made the *N*-alkyl and *O*-alkyl derivatives of *o*-aminophenoxyacetic anhydride from the potassium and silver salts. Comstock

¹ Am. Chem. J., **12**, 493 (1890).

² Ber. d. chem. Ges., **18**, 1529.

³ Am. Chem. J., **20**, 555.

and Wheeler,¹ however, soon found that silver succinimide, when treated with an alkyl halide in the cold, gives some *N*-ester along with the *O*-ester. Both Claisen² and Michael,³ moreover, had already found that sodium acetacetic ester gives with chlorcarbonic ester chiefly the *O*-derivative and a small amount of the *C*-derivative, whereas this salt and alkyl halides always give apparently only *C*-derivatives. Nef⁴ later found that potassium cyanide always gives a mixture of nitrile and isonitrile, and silver cyanide sometimes gives both compounds. The mere assumption of one structure for the alkali salt, and another for the silver salt, is obviously insufficient to explain these reactions and has in fact long been abandoned by most writers. Sodium acetacetic ester gives with acetic anhydride⁵ or with acid chlorides⁶ a mixture of *O*- and *C*-derivatives and the copper salt behaves in similar manner. If the free ester is heated with silver oxide and an alkyl halide, a mixture of the *O*- and *C*-alkyl derivatives is obtained,⁷ the former to the extent of about 5 per cent. The sodium salt⁸ of acetylacetone, benzoylacetone, etc., gives with acid chlorides a mixture of the *O*-acyl and *C*-acyl derivatives, and the silver salt of acetylacetone or of diacetylacetic ester gives, when treated with ethyl iodide, a mixture of the *O*-ethyl and *C*-ethyl derivatives. Bogert⁹ and Seil have published a fine review of the literature on analogous reactions of quinazolines, oxylepidines, etc., to which the reader is referred. The behavior of the potassium and silver salts of the urazoles, now worked out, is in complete accordance with these facts. Whichever salt we use, a mixture of *N*- and *O*-esters is obtained, although one may be formed in much greater amount; and furthermore, *in many cases, the*

¹ Am. Chem. J., **13**, 520 (1891).

² Ber. d. chem. Ges., **21**, 3397, 3567 (1888).

³ J. prakt. Chem., [2] **37**, 473 (1887).

⁴ Ann. Chem. (Liebig), **270**, 329 (1892).

⁵ Ber. d. chem. Ges., **25**, 1046 (1892). Ann. Chem. (Liebig), **278**, 223 (1894).

⁶ Ann. Chem. (Liebig), **277**, 182 and 199 (1893).

⁷ J. Chem. Soc., **77**, 739 (1900).

⁸ Claisen: Ber. d. chem. Ges., **25**, 1760. Nef: Ann. Chem. (Liebig), **276**, 232; **277**, 59; **287**, 269. Curtiss: THIS JOURNAL, **17**, 435. Dieckmann: Ber. d. chem. Ges., **33**, 2002; **37**, 3370, 3384, 3392, 4627; **38**, 2977; **39**, 3052. Lapworth: J. Chem. Soc., **93**, 30.

⁹ J. Am. Chem. Soc., **29**, 517; **31**, 507.

one present in smaller amount would easily have been missed if I had not looked for it. It is, therefore, not too much to say that it is probable that in the reactions of many, if not all, tautomeric compounds with reagents with which they could easily form two classes of derivatives—*O*- and *N*-, or *O*- and *C*-compounds, or others as the case may be—both are actually formed, although the amount of one may be in many cases too small to be easily detected. Comstock and Clapp¹ prepared a large number of *N*- and *O*-alkyl derivatives of anilides and toluides from the sodium and silver salts, respectively, and described the products obtained as pure, but, as far as their experimental data show, compounds of both classes could easily have been present in every case. Claisen² claims that sodium formanilide with ethyl iodide gives only a *N*-alkyl derivative, but the experimental data of the men³ from whom he quotes do not justify this statement.

Another difficulty confronting those who advanced the above theory lies in explaining the formation of an *O*-silver salt from a *N*-sodium salt by the direct action of silver nitrate on the sodium salt in solution. But, as stated above, this theory has been largely given up, since it is of little, if any, assistance in explaining the phenomena of tautomerism. Not so, however, with the idea that the salts have a single definite structure, namely, that of the stronger of the two tautomeric acids, or of the enol form of amides, acetacetic ester, etc. That view is still held by the majority of workers in this field. The difficulty then arises in explaining the formation of two alkyl, acyl, etc., derivatives directly from a single salt, and the theories put forward in the attempt to explain these reactions will be taken up in the next two sections.

II. The Rearrangement Theory.

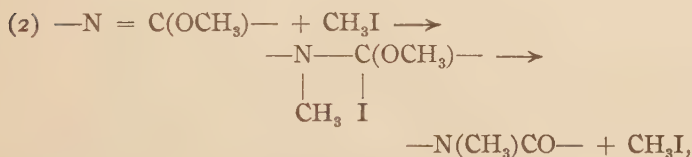
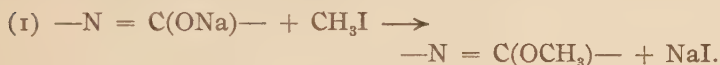
In most of the work referred to above not very much attention was paid to the effect that temperature or solvent may have on the products obtained. The silver salts were generally

¹ Am. Chem. J., **14**, 525 (1892).

² Ann. Chem. (Liebig), **287**, 361 (1895).

³ Ber. d. chem. Ges., **20**, 2273 (1887); **21**, 1106 (1888).

allowed to react¹ in the cold, usually in ether or benzene solution, while the alkali salts were as a rule heated in alcohol or mixtures of alcohol and water.² In 1899, Wheeler³ attempted to prepare the *O*-ester of formanilide by heating the silver salt with ethyl iodide at 100° to save time. It had formerly been prepared from the silver salt in the cold. Wheeler obtained only the *N*-ester. He then investigated the behavior of a large number of imido esters when they were heated with alkyl halides,⁴ and found that in nearly all cases they rearranged into *N*-esters. This beautiful work by Wheeler is of the very greatest importance in tautomerism, and must be considered in all alkylation, acylation, etc., reactions of tautomeric and other substances. He did not try to rearrange ethylphenylimido ester into the ethyl formanilide obtained above, but the reactions studied were exactly analogous. He therefore concluded that the *N*-alkyl esters in general are formed by rearrangement of *O*-esters first formed,



and made the following statement:⁵

“The tautomeric reaction in these cases, as in others, is undoubtedly nothing but one of addition.” Although Wheeler held to the addition theory in general, the context shows that he here had in mind the addition of alkyl halide to an *O*-ester first formed and a subsequent rearrangement of that addition product into a *N*-ester and the alkyl halide. The same author later studied other rearrangements, taking up, among other compounds, the imido acid anhydrides; the following quota-

¹ Am. Chem. J., **13**, 525 (1891).

² *Ibid.*, **13**, 514.

³ *Ibid.*, **21**, 185 (1899).

⁴ *Ibid.*, **23**, 135 (1900); **21**, 185 (1898); **30**, 28.

⁵ *Ibid.*, **21**, 187 (1899).

tion shows the conclusions reached:¹ "The results now at hand afford a satisfactory explanation for the behavior of sodium and silver salts of the amides and anilides with acid anhydrides and acyl chlorides. . . . In both cases imido-acyl anhydrides are formed as the first step of the reaction. Instead of the chloride acting by addition, as previously supposed, the acyl group directly replaces the metal. The products in the former case decompose at ordinary temperatures, while those in the latter rearrange into *N*-derivatives. *The action is similar to that of the alkyl halides, but the imido acid anhydrides undergo a molecular rearrangement with far greater ease than the imidoesters*" (italics ours). A similar view has been held by others. Claisen² found that the *O*-acetylacetic ester, when heated with potassium carbonate in ethyl acetate as solvent, was rearranged into the *C*-acetyl derivative, and that the reaction was accelerated by the presence of sodiumacetic ester. He concluded that this rearrangement furnished the explanation of the formation chiefly of the *C*-derivative in the acylation of the sodium salt by acetyl chloride.

Furthermore, a large number of *O*-esters of quinazolines,³ α -quinolones,⁴ pyridones,⁵ antipyrines,⁶ γ -oxyquinolines,⁷ etc., rearrange *catalytically* into the *N*-esters when heated alone or with alkyl halides. In these cases Knorr, especially, showed that the catalytic action of the alkyl halide is due to the formation of an intermediate double compound (as in probably most cases of catalysis) between the *O*-ester and alkyl halide, which decomposes into the *N*-ester and the alkyl halide.

In none of these cases, however, is the evidence conclusive, although it certainly is convincing. The mere fact that rearrangement may take place is no proof that it alone is accountable for the formation of the two products. It was not proved in the above cases that the rearrangement takes place

¹ Am. Chem. J., **30**, 28 (1903).

² Ber. d. chem. Ges., **33**, 3778 (1900).

³ Bogert and Seil: J. Am. Chem. Soc., **29**, 517.

⁴ Knorr: Ber. d. chem. Ges., **30**, 929. Ann. Chem. (Liebig), **236**, 106; **293**, 1.

⁵ Haitenger and Lieben: Monats. Chem., **6**, 322.

⁶ Knorr: Ann. Chem. (Liebig), **293**, 1. Ber. d. chem. Ges., **30**, 922, 927, 929, 933.

⁷ Knorr: Ber. d. chem. Ges., **30**, 937. Wenzel: Monats. Chem., **15**, 453.

rapidly enough to account for the amounts of the different compounds obtained. If these investigators had carried out the alkylation of silver formanilide and the rearrangement of ethyl phenylformimido ester under the same conditions of temperature, solvent, etc., and had studied the velocities of the reactions, it could then have been determined whether the amount of *N*-ester present was equal to that which should have been formed from the *O*-ester by rearrangement. Dieckmann¹ has criticized the above work of Claisen from this standpoint and in a preliminary paper has given results which indicate that the amount of *C*-acetyl derivative obtained by acetylation of sodium acetacetic ester is much greater than that obtained from the rearrangement of the *O*-acetyl body *under the same conditions*. It is necessary that experiments of this sort should be carried out quantitatively if the conclusions drawn from them are to be valid.

The results of my work on the urazoles show in two entirely different ways that the rearrangement hypothesis will not account for the phenomena here observed.

*In all the alkylation experiments carried out quantitatively under varying conditions, from each salt a mixture of N- and O-esters in practically a constant ratio was formed.*² The potassium salt of 1-phenyl-4-methylurazole was treated with one molecule of ethyl iodide in a mixture of ethyl alcohol-water at 25°, 60°, and 90°; the silver salt with one or two molecules of ethyl iodide in ether at 60° and 90°. In every case except in the experiment at 25° the reactions were complete in a few hours. If the *O*-ester rearranged into the *N*-ester the ratio of the amounts of these two esters would vary with the time; since no such variation was observed we can only conclude that the *O*-ester does not rearrange appreciably. All attempts to cause a rearrangement of the *O*- into the *N*-derivative, or *vice versa*, have, moreover, been unsuccessful.³ The *O*-esters, heated with ethyl iodide

¹ Ber. d. chem. Ges., **37**, 3392 (1904).

² Dr. J. M. Johnson has studied (1906-8) the alkylation of the potassium, sodium, barium, zinc, cadmium, mercury, cobalt, nickel, and other salts of 1-phenyl-4-methylurazole and obtained the same result.

³ Dr. J. M. Johnson has now obtained evidence that the 1-phenyl-3-allyloxy-4-methylurazole can be changed at 100° into the corresponding 2-allyl derivative.

during 24 hours at 90° in alcohol and water, did not rearrange. In this case, however, the iodide was probably decomposed by the solvent in a few hours. To avoid this decomposition the experiment was repeated in ether and the temperature was kept at 200° for two hours; here again no rearrangement was detected. Furthermore, some of the alkylation experiments by Dr. J. M. Johnson, in which the *O*- or *N*-ester, urazole salt and alkyl halide were heated together under the conditions attending the alkylation experiments, furnish still more evidence on this point and show, as well, that the rearrangement does not take place in the opposite direction. They also answer the objection, which might be raised, that in the above experiments instituted to cause rearrangements the exact conditions existing during the alkylation were not reproduced. In some of the experiments with the silver salt, two molecules of the ethyl iodide were used. Some of the tubes, as the data show, were opened when the reaction had been under way only a short time while others were heated long after the alkylation process was complete. With the excess of ethyl iodide present there was every opportunity for rearrangement, yet the relative amounts of the two products was the same in all cases, within the limits of experimental error. The only way of reconciling these facts with the rearrangement theory would be to assume that the rearrangement reaction is instantaneously reversible, perhaps on account of some special catalytic action of some substance present. This possibility, which is very improbable in any case now known, would not harmonize with the fact that the ratio obtained from the potassium salt is greatly different from that yielded by the silver salt, and is disproved in Dr. J. M. Johnson's work by special experiments instituted to test this point by adding *O*-ester and *N*-ester to the alkylation mixture; the ratio of the amounts of these two esters was very close to that calculated on the assumption that no rearrangement takes place. If any rearrangement takes place in our experiments it is so small in amount that it cannot possibly account for the amounts of *N*-ester and *O*-ester obtained.

The Addition Theory.

Another theory used to-day as a correlation of the phenomena of tautomerism is the "addition theory" first proposed by Michael,¹ and since then upheld, at times, in the same general form by Nef² and others. Nef³ has given up his views on this theory. According to Michael's conception the molecular form of the amide salts adds the alkyl halide and a mixture of the *N*-ester and *O*-ester is formed from this double compound. This theory looks very plausible when viewed from Michael's standpoint and when only qualitative facts are considered, but seems very improbable when all the *quantitative facts* known to-day are scrutinized.

Michael does not use the facts at the bottom of the ionization theory in connection with the "addition theory," but believes that the undissociated salts add the alkyl halide and that this double compound then yields the *N*-ester and *O*-ester. Others in this laboratory have secured a large amount of experimental evidence showing that the *ions and the molecules* of the salt are both concerned in some of these reactions, and hence Michael's theory is weak in this respect.

The following examples, among many others, will suffice to show why I do not believe that Michael's theory can be a general correlation of the known facts. 1-Phenyl-3-thiourazole reacts readily with methyl iodide and ethyl iodide when 0.05 N solutions of each are mixed at 50°. Now the hydriodic acid liberated in the reaction



causes a suppression of the ionization of the fairly strong thiourazole acid ($K = 0.017$) and hence a *relative increase in the per cent. of the molecular form of the acid*. If, as Michael believes, only the molecular form of the acid reacts with the alkyl halide, *the reaction velocity should increase. As a matter of fact, the reaction velocity decreases very greatly, as is to be predicted from our theory, which will be discussed later.* The

¹ J. prakt. Chem., **37**, 469; **45**, 580; **46**, 189, and many later papers, especially Am. Chem. J., **43**, 322; Ber. d. chem. Ges., **43**, 621.

² Ann. Chem. (Liebig), **266**, 52; **276**, 200; **277**, 59, 83, etc.

³ *Ibid.*, **298**, 263.

following table, worked out by Dr. G. H. Shadinger,¹ will illustrate this point:

0.05 Volume Normal² 1-Phenyl-3-thiourazole + 0.05 Volume Normal Ethyl Iodide in 50 Per Cent. Alcohol at 50°.

Shadinger.

t. Min.	A.	A-X.	X.	A ₁ K ₁ .	K ₁ .
5	4.90	4.11	0.79	0.0392	1.568
10	4.90	3.57	1.53	0.0380	1.520
15	4.90	3.18	1.72	0.0367	1.468
31	4.90	2.46	2.44	0.0325	1.300
60	4.90	1.88	3.02	0.0273	1.096
120	4.90	1.29	3.61	0.0238	0.952

In the same way the addition of potassium iodide, for example (and other salts), should increase the per cent. of the molecular form of potassium (or other) urazoles in solution with alkyl halides and hence, if Michael's theory were correct, cause an increase in the reaction velocity. *As a matter of fact, in every case that I have studied, with one or two exceptions, the velocity is decreased to about the extent to be predicted from my theory.*³

Although a great many of Michael's ideas are very helpful in these problems, and he is without doubt one of our most brilliant organic chemists, it seems to me that the elemental weakness of his position is the failure to harmonize the facts of modern physical chemistry with his own ideas on the theory of organic reactions.

The Theory of Tautomeric Salts.

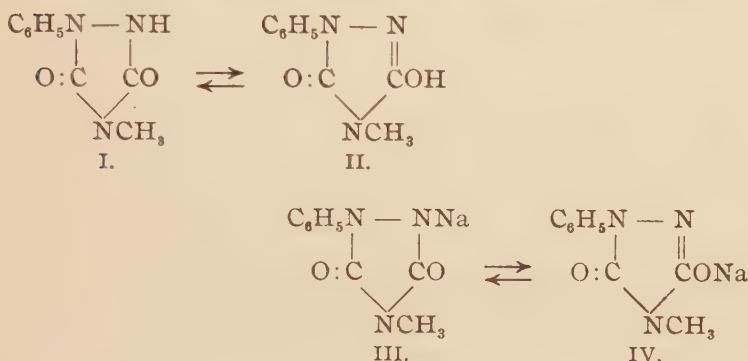
I took up this problem with the idea of securing evidence

Am. Chem. J., **39**, 271. Ber. d. chem. Ges., **41**, 3234.

² The values A_1K_1 and K_1 are calculated on the normal basis; i. e., on the basis that A is 5.00 instead of 4.90 (*loc. cit.*).

³ A large number of other weak points in Michael's theory will be discussed soon in an answer to his recent criticism of our urazole work (Am. Chem. J., **43**, 322. Ber. d. chem. Ges., **43**, 621). Mr. H. C. Robertson has now shown by measuring the ionization of sodium phenolate and its velocity of reaction with methyl iodide and ethyl iodide in absolute alcohol, that the phenolate ions react about 7 times as rapidly as the sodium phenolate molecules (or, what is kinetically equivalent, the sodium ions and the phenolate ions together). Mr. S. K. Loy has shown the ethylate ions and sodium ethylate molecules (*vide* preceding parenthesis) to react with about the same velocities with methyl iodide.

on the three theories already discussed and on the theory of tautomeric salts. It seemed possible that both the imide and the enol group of the two tautomeric forms, (I) and (II), of 1-phenyl-4-methylurazole could give salts which should react with alkyl halides. Such imide salts as potassium¹ pyrrole and alkali



salts of aniline² and diphenylamine act readily, violently in some cases, with alkyl halides, and the pyrrole salts also react with acid chlorides.³ The enol salts should react with alkyl halides in a manner analogous to the formation of esters from the sodium salts of organic acids and alkyl halides. *It seemed possible then that in all cases in which these tautomeric urazoles give two or more stable isomeric products as the result of a reaction they do so because they exist in two or more tautomeric forms in equilibrium, each of which reacts independently, or because one form is changed into stable derivatives through two or more side reactions.*

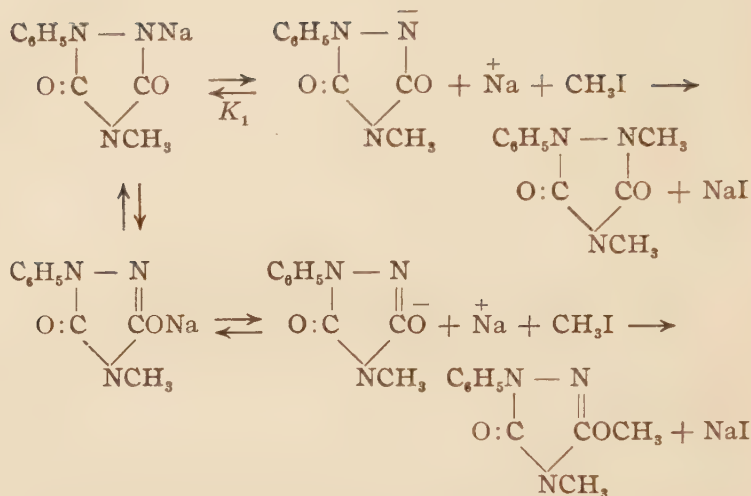
If there are two salts whose molecules are in equilibrium, the reaction may be expressed graphically⁴ as follows:

¹ Ber. d. chem. Ges., **17**, 2951.

² *Ibid.*, **6**, 1514.

³ *Ibid.*, **18**, 881.

⁴ *Ibid.*, **41**, 3199.



Let the concentration of the total urazole salt be represented by $C_{\text{urazole salt}}$, that of the alkyl halide by $C_{\text{alkyl halide}}$, that of the undissociated keto salt by C_{km} , that of the keto ions by C_{ki} , that of the undissociated enol salt by C_{em} , and that of the enol ions by C_{ei} , and assume that the value of K_3 in the equation $K_3 = \frac{C_{km}}{C_{em}}$ remains practically constant during the reaction. Let x be the concentration of *N*-ester and x_1 that of the *O*-ester formed in the time t . Then the following equations must hold:

$$\frac{dx}{dt} = k_{\text{trans}} (C_{\text{urazole salt}} - x - x') (C_{\text{alkyl halide}} - x - x') \dots \quad (1)$$

$$\frac{dx'}{dt} = k_1'_{\text{trans}} (C_{\text{urazole salt}} - x - x') (C_{\text{alkyl halide}} - x - x') \dots \quad (2)$$

$$\frac{d(x + x')}{dt} = (k_{\text{trans}} + k_1'_{\text{trans}}) (C_{\text{urazole salt}} - x - x') (C_{\text{alkyl halide}} - x - x') \quad (3)$$

$$\frac{k_{\text{trans}}}{k_1'_{\text{trans}}} = \frac{x}{x'} = \frac{\text{N-ester}}{\text{O-ester}} \dots \dots \dots \quad (4)$$

It makes no difference whether the undissociated salt, or the ionized portion, or both, are reacting with the alkyl halide; the equations still hold and we then have $K_{trans} = K_{mol} C_{km} + K_{ion} C_{ki}$ and $K'_{trans} = K'_{mol} C_{em} + K'_{ion} C_{ei}$. These equations are based on the assumption that Arrhenius' ionization theory holds more accurately than my experimental data.

(1) This theory of tautomeric salts then leads us to the conclusion that the total ester, *N*-ester + *O*-ester, as well as the *N*-ester and the *O*-ester, individually, must be formed with a velocity expressed by a reaction of the second order. This I have found to be true for the potassium salt (page 545), and Dr. J. M. Johnson has shown it to hold for a number of other salts.

(2) According to these equations the ratio *N*-ester : *O*-ester should be a constant throughout the reaction. This has been found true of both the potassium and the silver salts, as can be seen on page 546, 547.

(3) If the values of K_{mol} , K'_{mol} , K_{ion} , K'_{ion} , $C_{ei} : C_{em}$, and $C_{ki} : C_{km}$, vary with different salts, then different ratios of *N*-ester : *O*-ester might be obtained from different salts. I have found this to be true of the potassium and silver salts, and Dr. J. M. Johnson showed the same for a large number of other salts. The ratio *N*-ester : *O*-ester for the potassium salt is about 91 : 9 at 60° in 40 per cent. alcoholic solution, and about 38 : 62 for the silver salt at 60° in ether.

The work presented in this paper does not give absolute evidence on the question whether the ions or the undissociated salts react with the alkyl halides but observations recently made by Dr. F. M. Rogers (1908), Mr. H. C. Robertson (1909-1910), and Mr. S. K. Loy (1909-1910), in this laboratory show that both ions and molecules are reacting in certain cases. When both ions and molecules are appreciably concerned in the reactions we may find corresponding variations in the ratios of esters, reaction velocities, and changes in concentration. All the facts presented in this paper are in harmony with the idea of two tautomeric salts in instantaneous equilibrium, and, taken in connection with the recent work, give

very strong evidence in favor of this view. The entire question will be discussed fully in a subsequent article.

At the outset of this work a study of the alkylation of potassium phenylurazole by various alkyl iodides was made and by this means a number of derivatives with radicals at position 2 were prepared. In former work it had been noted that the products from the action of alkyl iodides on the potassium and silver salts were never pure, and Acree had already suspected that alkylation took place at more than one position. My first aim was to see if there was evidence that some *O*-ester was also formed from the potassium salt along with the main product—the *N*-ester. It was also thought possible that some of the higher alkyl derivatives would have such solubilities that they would be easier to separate and purify than the methyl and ethyl compounds, and that my investigation could thus be made much easier. In most cases it was proved that some *O*-derivative was present, but in these experiments I could not isolate the compounds in pure enough condition to determine exactly how much, and it is quite possible that in the cases where no evidence of its presence was found it was missed by some error in manipulation. It was also discovered later that the reaction mixtures were heated much longer than was necessary and that the excess of alkali used in some cases produced a partial decomposition of the compounds—probably a breaking open of the urazole ring. In the case of the isobutyl and isoamyl compounds only a trace of *O*-derivatives was detected. In the other cases, the amount appeared to be from 10 to 20 per cent. of the total alkylated product.

The melting points of these compounds as given below are of some interest. It is to be noted that if we except the methyl derivative, which generally melts higher than the corresponding ethyl derivative, the melting points of the urazoles having substituting groups with normal carbon chains increase as the weight of the radical increases, while the melting points of branching chain derivatives decrease with increase in weight of the substituting radical:

1-Phenyl-2-methylurazole, 184°–185°.

1-Phenyl-2-ethylurazole, 119°.5.

1-Phenyl-2-*n*-propylurazole, 128°.5.

1-Phenyl-2-*n*-butylurazole, 130°.

1-Phenyl-2-isopropylurazole, 161°.5.

1-Phenyl-2-isobutylurazole, 153°.

1-Phenyl-2-isoamylurazole, 97°.

Much more accurate analytical results were obtained in the alkylation of the salts of 1-phenyl-4-methylurazole. The method is liable to an error of two or three per cent. but, considering the difficulty naturally attending the quantitative separation of organic compounds having about the same solubilities, it is very satisfactory and will be shown to be accurate enough to justify the conclusions drawn. In the alkylation of potassium 3-thiourazole the results are still more accurate as the course of the reaction can here be followed by titration methods.

EXPERIMENTAL.

Phenylurazole.—Phenylurazole was prepared according to the method described by Acree.¹ It melts at 261°–262° and is practically insoluble in benzene, ligroin, carbon tetrachloride and chloroform as was determined in the following manner: Five-tenths of a gram of substance was allowed to stand with 10–12 cc. of each solvent for twenty-four hours at room temperature, being shaken at intervals. The solution was then filtered into a weighed porcelain dish and quickly weighed. After evaporation of the solvent the residue was weighed.

	Benzene.	Ligroin.	Carbon tetrachloride.	Chloroform.
Wt. solution	9.11	6.25	11.91	13.91
Wt. residue	0.0015	0.00	0.0005	0.00

The solubility in benzene, which is the greatest, is thus less than one part in five thousand.

Phenylurazole is acid to phenolphthalein, which was used in all titrations unless otherwise specified. The alkali used was in all cases potassium hydroxide.

¹ Am. Chem. J., **27**, 126 (1902).

1-Phenyl-2-methylurazole.—This had already been prepared by Acree¹ by the action of methyl iodide on potassium phenylurazole. A product melting at 185° was obtained by this method. It was also prepared by dissolving potassium phenylurazole in water and shaking with an excess of dimethyl sulphate. The alkylated product gradually separated out and was filtered off. It was separated from phenylurazole by extraction with chloroform. It melted at 183° and, after one crystallization from water, the melting point was 185°–186° and this was not changed on mixing the substance with that obtained by use of methyl iodide. Analysis:

0.1241 gram substance gave 24.5 cc. nitrogen at 25°.8 and 764.9 mm.

	Calculated for $C_9H_9O_2N_3$.	Found.
N	22.03	22.22

In the following alkylation experiments I expected to obtain:

(1) Unchanged phenylurazole, because the hydriodic acid, from the hydrolysis of the alkyl iodide, would liberate phenylurazole from the salt.

(2) 2-*N*- and 3-*O*-alkyl derivatives.

(3) Traces of 5-*O*- and of 4-*N*-alkyl derivatives which it would have been so difficult to separate from the 2-*N*-compounds that this was not attempted; and

(4) The various possible dialkylated products.

The general method of isolating these products was to evaporate the solution to small bulk at the end of the experiment, filter off the substance which separated out, and extract it, when dried, with chloroform. This left undissolved any regenerated phenylurazole, together with inorganic substances, but dissolved all of the alkylated products. The chloroform was evaporated and the residue was then taken up in alkaline solution, in which the monoalkyl derivatives are soluble; any insoluble dialkylated products were extracted by ether or chloroform.

The monoalkyl derivatives were then precipitated by acid-

¹ Am. Chem. J., **27**, 128 (1902).

fying the alkaline solution, filtered off and evaporated to dryness several times with concentrated aqueous hydrochloric acid and sufficient alcohol to bring them into solution, in order to convert into phenylurazole any *O*-alkylurazole present. A second extraction with chloroform then left behind any phenylurazole so formed. Evaporation of the chloroform solution should then give only 2-*N*- together with a little 4-*N*-alkyl derivative and some impurities. The main product was obtained pure by repeated recrystallization, precipitation from alkaline solution, etc., as described below.

1-Phenyl-2-ethylurazole.—Five grams of phenylurazole in 35 cc. alcohol were titrated with 0.9 N potassium hydroxide (about 30 cc.); 5.6 grams (1.25 molecules) ethyl iodide were added and the solution was made up to 100 cc. with alcohol. This was heated 4.5 hours on the water bath under a return condenser. About one-third of the solvent was then evaporated off and, on cooling, 0.8 gram phenylurazole, melting at 262°, crystallized out. Ethyl iodide is decomposed by water and gives hydrogen iodide; this would account for the liberation of phenylurazole. The solution was evaporated to about 15 cc. and an oil separated out, which solidified when cooled and rubbed. This was recrystallized from hot alcohol, the iodine being removed by thiosulphate. Its melting point was not sharp, about 88°. Extraction with chloroform left 0.2 gram substance melting at 235° (impure phenylurazole), while evaporation of the chloroform solution gave 3.5 grams substance melting at 101°, still not sharply. For the neutralization of 0.1023 gram of this product 5.34 cc. 0.907 N alkali, instead of the calculated 5.50 cc., were required. The main portion was then evaporated twice to dryness in an open dish with alcoholic hydrochloric acid in order to convert any ethoxy body present into phenylurazole. Extraction with chloroform then left 0.4 gram phenylurazole melting at 262°, and evaporation of the chloroform gave a substance melting at 110°–116°. This was extracted four times with the same lot of water (50–75 cc.) at 50° and allowed to crystallize each time at 0°. The fractions so obtained melted at 117°.5, 118°, 119°, 119°, respectively, but all softened at about 115°. The

whole amount, weighing 0.2106 gram, was titrated with 0.907 N alkali. Calculated, 11.32; required, 11.12 cc.

The substance was then precipitated in two fractions by sulphuric acid. The second fraction was purer. It softened at 117° and melted at 118°.5–119°. These last two lots weighed together 1.7 grams. On evaporation of the acidified solution to a small bulk crystals melting at 80°, but in too small amount for identification, separated out.

Five grams of phenylurazole thus gave 1.0 gram unchanged material, 3.5 grams alkylated product, 0.5 gram ethoxy derivative, and 2.1 grams pure 2-*N*-ester, melting at 119°. Analysis:

0.1246 gram substance gave 22.95 cc. nitrogen at 25°.8 and 765 mm.

	Calculated for $C_{10}H_{11}O_2N_3$.	Found.
N	20.53	20.73

This ethyl derivative is easily soluble in ether, chloroform, hot alcohol and hot water; difficultly soluble in cold water or alcohol.

Silver Salt.—About 0.3 gram substance was titrated with alkali; and then one equivalent of 0.1 N silver nitrate solution was added. The precipitate formed redissolved until about one-half the required amount of silver nitrate had been added, then became permanent. This phenomenon has been observed in many other cases in my urazole work, and indicates that a *soluble* alkali-silver double salt is present in solution. The solution was boiled, then cooled, and the salt was filtered off. Dried at 100°, it darkened very slightly and then melted at 259°, apparently with little decomposition. Analysis:

0.1143 gram substance gave 0.0399 gram silver.

	Calculated for $C_{10}H_{10}O_2N_3Ag$.	Found.
Ag	34.58	34.97

1-Phenyl-2-n-propylurazole.—To 5 grams phenylurazole, neutralized with alkali, were added 20 cc. alcohol and 6 grams (1.25 mols.) *n*-propyl iodide. The solution was heated to boiling under a return condenser for eleven hours, then the

product worked up as in the case of the 2-*N*-ethyl derivative described above. After hydrolysis of the *O*-esters present and removal of the phenylurazole so formed, a small amount of substance insoluble in alkali was found. The alkaline solution was extracted twice with ether and evaporation of this ether solution gave a small amount of oil, perhaps di-*N*-ester. The alkaline solution was acidified fractionally and gave four lots of propyl derivative varying in melting point from 127° to 128°.5. The whole amount was recrystallized from 50 per cent. alcohol and 2.4 grams, melting at 128°, were obtained.

Five grams of phenylurazole thus gave 0.4 gram regenerated phenylurazole, 5.3 grams crude alkylated product, 0.86 gram *O*-ester, a trace of 2,4-di-*N*-ester, and 2.4 grams pure *N*-ester, melting at 128°. Analysis:

0.1205 gram substance gave 20.2 cc. nitrogen at 27°.5 and 762 mm.

	Calculated for $C_{11}H_{13}O_2N_3$.	Found.
N	19.27	18.63

Silver Salt.—Two lots of this salt were prepared by the same procedure described for the ethyl derivative. In the first case two drops of alcoholic phenolphthalein were used for the alkali titration and the silver salt turned dark before filtration. The experiment was repeated and solid phenolphthalein was used. The melting points of the two specimens were not sharp and did not agree, being 132° and 150°. Both, however, gave fairly good analyses:

I. 0.1049 gram substance gave 0.0348 gram silver.

II. 0.1754 gram substance gave 0.0577 gram silver.

	Calculated for $C_{11}H_{12}O_2N_3Ag$.	I.	Found.	II.
Ag	33.10	33.27		32.90

1-Phenyl-2-n-butylurazole.—Five grams of phenylurazole were titrated with alkali and 10 cc. alcohol and 6 grams (0.5 mols.) *n*-butyl iodide added. This solution was heated to boiling for ten hours under a return condenser. Ten cc. more alcohol were added and the heating was continued twenty

hours longer. The procedure was practically the same as for the ethyl and propyl derivatives. The final product was dissolved in alkali and precipitated in five fractions. These melted at about the same point, the first two sharply at 130° , while the others softened at $125^{\circ}.5$. The melting point is very close to that of the propyl derivative above (128°), but a mixture of the two melted at 123° .

Five grams of phenylurazole, then, gave 0.9 gram unchanged substance, 3.1 grams crude product, 0.35 gram *O*-ester, a trace of 2,4-dialkyl derivative, and 1.3 grams pure 2-*N*-ester, melting at 130° . Analysis:

0.1304 gram substance gave 21.1 cc. nitrogen at $27^{\circ}.5$ and 762 mm.

	Calculated for $C_{12}H_{15}O_2N_3$.	Found.
N	18.06	18.00

1-Phenyl-2-isopropylurazole.—Five grams of phenylurazole were neutralized with alkali, 6.2 grams (1.25 mols.) isopropyl iodide and 10 cc. alcohol were added, and the mixture was heated to boiling for five hours. The treatment of the product was the same as in the above cases. The product finally obtained melted at $161^{\circ}.5$, softening at 160° . An attempt was made to prepare a silver salt, but it came down in such gelatinous condition that it could not be separated out pure.

Five grams of phenylurazole, then, gave 2.2 grams unchanged phenylurazole, 2.5 grams crude product, 0.69 gram *O*-ester, and 0.75 gram *N*-ester. Some was lost. After the hydrolysis with acid a trace of product insoluble in alkali—di-*N*-alkyl derivative—was present. The *N*-ester melted at $161^{\circ}.5$.

1-Phenyl-2-isobutylurazole.—Five grams phenylurazole were neutralized with alkali. To this were added 6 grams isobutyl iodide and 30 cc. alcohol, and the mixture was heated to boiling under a return condenser twenty-eight hours. The procedure was the same as in the preceding cases.

Five grams substance gave 2.5 grams unchanged phenylurazole, a trace of *O*-ester, a trace of di-*N*-derivative, and 1.2 grams pure 2-*N*-ester, melting at $152^{\circ}.5$, first softening at 149° . Analysis:

0.1301 gram substance gave 21.35 cc. nitrogen at 27°.5 and 762 mm.

	Calculated for $C_{12}H_{16}O_2N_3$.	Found.
N	18.06	18.24

Silver Salt.—1-Phenyl-2-isobutylurazole, weighing 0.3147 gram, was titrated with 0.101 N alkali, 13.52 cc. being required instead of the calculated 13.37 cc. One molecule of silver nitrate was added and the solution was boiled to make the precipitate filter more readily. No definite melting point could be obtained. The salt contained too large a percentage of silver. Analysis:

I. 0.1531 gram substance gave 0.0499 gram silver.

II. 0.1812 gram substance gave 0.0542 gram silver.

	Calculated for $C_{12}H_{14}O_2N_3Ag$.	I.	Found.	II.
Ag	31.73	32.59		33.68

1-Phenyl-2-isoamylurazole.—Five grams phenylurazole were titrated with alkali, 10 cc. alcohol and 7 grams isoamyl iodide were added, and the whole was boiled twenty-one hours. The procedure was the same as above. The total yield of pure 2-*N*-isoamylurazole melting at 97°–98° was 1.5 grams. Under water the substance became liquid at 75°. In every case it separated from the solvent—chloroform or alcohol—as an oil which solidified on cooling.

Five grams phenylurazole gave 4.1 grams crude product, 0.3 grams unchanged phenylurazole, a slight amount of *O*-ester and of the 2,4-di-*N*-ester, and 1.5 grams pure 2-*N*-isoamyl derivative, melting at 97°–98°. Analysis:

0.1429 gram substance gave 21.62 cc. nitrogen at 26°.5 and 761 mm.

	Calculated for $C_{13}H_{17}O_2N_3$.	Found.
N	17.04	16.86

Experiments described below indicate that these reactions were in every case complete in a few hours, so that the long heating was superfluous. The 2-alkyl derivatives obtained above are all easily soluble in chloroform and benzene, diffi-

cultly in water, more readily in alcohol. These solubilities all appear to decrease slightly with increase in the weight of the alkyl groups. In every case some 3-*O*-alkyl derivative was formed, but the amounts found should not be taken as exact since a quantitative method of separating the products had not then been worked out. In nearly every case some material insoluble in alkali was present, but the quantity was never sufficient for investigation. Later experiments, however, have shown that the 2-ethyl-4-methyl compound, at least, is volatile on the water bath, so that the amount of dialkyl product formed in any case may have been greater than the results indicate.

Action of Ethylene Dibromide.—Five grams of phenylurazole were neutralized with alkali and heated with two molecules of ethylene dibromide in 40 per cent. alcohol for twenty hours. Considerable phenylurazole was recovered and a gum was also obtained which was soluble in ether and hot alcohol, somewhat soluble in hot water, and which gave, with copper oxide, a strong test for bromine. It was too impure and the amount was too small for further investigation. It was found that the flame test for bromine with copper oxide must be used with caution, since phenylurazole¹ gives a slight greenish color.

1-Phenyl-2,4-diethylurazole.—Five grams of phenylurazole were dissolved in three equivalents (about 85 cc.) of potassium hydroxide solution. To the solution three molecules (13.2 grams) ethyl iodide and 21 cc. alcohol were added. After boiling for eighteen hours the solution was nearly neutral, so one-half molecule more alkali was added and the boiling continued eighteen hours longer. The solution was then evaporated to dryness, a small amount of water was added, the solution made alkaline, and the insoluble oil, which appeared, separated by extracting five times with ether. Chloroform would have been better for this purpose.

The alkaline solution gave, on acidification, 2.5 grams of 1-phenyl-2-ethylurazole melting fairly sharply at 119°. Ex-

¹ Hugo Milrath (Chem. Ztg., **33**, 1249; Chem. Abs., **4**, 907) has recently called attention to the fact that other nitrogen compounds behave in this way. The Beilstein test for halogens should not be used in these cases, a direct method being preferable.

traction of this material with chloroform left only inorganic matter. After evaporation with hydrochloric acid no regenerated phenylurazole was obtained, but the material after one recrystallization from alcohol melted sharply at 119° – $119^{\circ}.5$. When mixed with 1-phenyl-2-ethylurazole melting at 119° , the melting point was unchanged.

Evaporation of the ether solution above gave an oil. This was evaporated several times with alcohol and hydrochloric acid, and the product extracted repeatedly with ether. This took up the oil and left no phenylurazole. The material at this point was a somewhat yellowish oil, soluble with some difficulty in ether, which would not solidify on being rubbed with ligroin. It was apparently, as would be expected, the 1-phenyl-2,4-diethylurazole. The fact that, although the phenylurazole was apparently completely alkylated, only 2–3 grams of product was obtained is due to decomposition of the compounds by the excess of alkali used. It is shown below that the 2-ethyl-4-methyl compound is decomposed to a considerable extent by standing at room temperature for twenty-four hours with a moderate excess of alkali. This fact accounts also for the poor yields in the attempts to prepare various 4-alkyl derivatives, in which an excess of alkali was always used. Analysis of the oil:

0.2205 gram substance gave 36.0 cc. nitrogen at $21^{\circ}.5$ and 750 mm.

	Calculated for $C_{12}H_{18}O_2N_3$	Found.
N	18.06	18.38

Alkylation in Absolute Alcohol.—Five grams of potassium phenylurazole were heated to boiling in absolute alcohol with 1.5 molecules ethyl iodide for eleven hours. The salt is only moderately soluble in alcohol. The material that first separated out was phenylurazole with 15–20 per cent. of alkylated product, but the melting point was only 10° – 12° lower than that of pure phenylurazole, although not at all sharp. No indication of the presence of any 3-ethoxy derivative was obtained. A product was isolated which melted at 116° , but when this was mixed with the 2-ethyl derivative melting

at 119° the mixture melted at 105°. Another product weighing less than 0.1 gram and melting at 84° was also isolated. The quantity of each of these was too small for further purification. The former may have been a mixture of the 2- and 4-ethyl derivatives.

Ethyl Carbethoxythioncarbamate.—This was prepared according to the method of Delitsch¹ and Wheeler.² The yield was poor in all cases. An attempt was made to purify the product by distillation in a vacuum, but at 20 mm. pressure only 2.5 grams of pure substance were obtained by distillation of 25 cc. of the oil, showing that decomposition must have taken place during the distillation. In one case it was attempted to isolate the product by pouring the reaction mixture directly into an alcoholic solution of 1.5 molecules of potassium hydroxide, but the yield of the thion compound, in that experiment, from 150 grams of ethyl chlorcarbonate, was only 30–40 grams. The best yield obtained was 85 grams from 100 grams of the chlorcarbonic ester, or about 50 per cent.

1-Phenyl-3-ethoxyurazole.—This was prepared by the method of Wheeler,³ who heated the carbethoxythioncarbamic ester with phenylhydrazine. The process should be carried out in an atmosphere of carbon dioxide to avoid, as far as possible, the formation of a deep red compound rather difficult to remove. This colored substance is difficultly, if at all, soluble in ether, somewhat more so in benzene; but it can best be removed by extracting the dry 1-phenyl-3-ethoxyurazole salt with alcohol. The ethoxy body obtained melted at 149°–150°. The melting point formerly obtained was 152°.⁴

1-Phenyl-3-ethoxy-4-methylurazole.—This was prepared by dissolving the ethoxy compound in a small excess of alkali and shaking the solution with somewhat of an excess of dimethyl sulphate. The water and alkali decompose the dimethyl sulphate, and 1-phenyl-3-ethoxyurazole is liberated, so that frequent addition of more dimethyl sulphate and alkali is

¹ J. prakt. Chem., [2] **10**, 118 (1874).

² J. Am. Chem. Soc., **22**, 377 (1900).

³ *Loc. cit.*

⁴ Ber. d. chem. Ges., **36**, 3146 (1903).

necessary. The alkylation product separates out and is filtered off. The melting point, without further purification, was 93° , that found formerly being 95° .¹ The yield was, however, only about 75 per cent. of the calculated, probably on account of decomposition of the material by the excess of alkali. This danger was not discovered until later in the work. Dr. J. M. Johnson has found that better yields are obtained if the solution of the urazole salt is heated to about 60° before the dimethyl sulphate is added.

This 4-methyl-3-ethoxy derivative is readily soluble in chloroform and carbon tetrachloride.

*1-Phenyl-4-methylurazole.*²—The above 1-phenyl-3-ethoxy-4-methylurazole was at once hydrolyzed by evaporation to dryness several times with alcoholic hydrochloric acid. This operation should be carried out in a closed tube to prevent loss. The resulting substance was dissolved in alkali, filtered, and precipitated by sulphuric acid. The melting point was 222° – 223° . It was extracted in a Soxhlet apparatus with alcohol, but both the portion soluble in alcohol and that left behind melted at the same point as before. This material was used for the quantitative experiments below. Addition of silver nitrate to a solution of the potassium salt precipitates a stable insoluble silver salt.

1-Phenyl-4-methylurazole is difficultly soluble in both cold chloroform and ether. The solubility in water was determined by dissolving a weighed amount of substance in alkali, precipitating with acid, filtering, and weighing. Of 0.1032 gram substance dissolved, in about 75 cc., 0.0891 gram was precipitated, therefore 0.0131 gram remained dissolved. The solubility is then about one part in 5,000 parts of the aqueous filtrate containing small amounts of inorganic substances.

Although the free 4-methyl compound is acid to phenolphthalein, its alkali salts, like those of phenylurazole, are alkaline to methyl orange so that the potassium salts can be titrated quantitatively with a strong acid when the latter indicator is used.

¹ Ber. d. chem. Ges., **36**, 3148 (1903).

² *Ibid.*, **36**, 3149 (1903).

I. 0.1032 gram substance required 5.71 cc. 0.0995 N alkali (phenolphthalein) instead of the calculated 5.43 cc. The potassium salt then present required 5.66 cc. 0.0989 N sulphuric acid (methyl orange) instead of 5.45 cc. calculated from the methyl compound or 5.75 cc. from the alkali.

II. 0.1033 gram substance required 5.71 cc. alkali, then 5.69 cc. acid.

1-Phenyl-4-ethylurazole.¹—Three grams of 1-phenyl-3-ethoxyurazole were heated with excess of alkali and of ethyl iodide for fifteen hours. After hydrolysis of the ethoxy group by hydrochloric acid a substance was isolated which was readily soluble in ether and chloroform, and could be recrystallized from alcohol. Its melting point was fairly sharp at 168°.5. The amount was too small for further work. As in the case mentioned above, the excess of alkali used decomposed a large part of the material.

1-Phenyl-4-n-propylurazole.—This was prepared like the 4-ethyl derivative above. The substance obtained was purified by recrystallization from alcohol. It melted at 120°, softening at 118°.

0.1160 gram required 5.32 cc. 0.0995 N alkali instead of the calculated 5.29 cc.

Analysis:

0.105 gram substance gave 17.4 cc. nitrogen at 10° and 750.4 mm.

	Calculated for $C_{11}H_{13}O_2N_3$.	Found.
N	19.21	19.57

1-Phenyl-4-n-butylurazole.—This was prepared like the above 4-alkyl derivatives. After hydrolysis by acid, extraction by chloroform, and recrystallization from alcohol, the product melted at 149°–150°, softening at 146°.

0.1130 gram substance required 4.93 cc. 0.0995 N alkali instead of the calculated 4.87 cc.

Only enough material for one analysis was obtained and that, unfortunately, was lost.

1-Phenyl-2-ethyl-4-methylurazole.—This was obtained from

¹ Busch and Heinrichs: Ber. d. chem. Ges., **34**, 2334.

the alkylation process below. The substance obtained from the potassium salt at 60° melted at 51° , softening at 49° . It was found to be easily soluble in ethyl and methyl alcohols, ethyl acetate, ligroin, toluene and acetone. It can be precipitated from methyl alcohol (but not from ethyl alcohol or acetone) by addition of water, and was purified in that way. It then melted at 52° – 53° . The analysis is given below on p. 544.

Constant Temperature Bath.

In studying quantitatively the alkylation of the urazole salts it was necessary to have a means of keeping small closed tubes at any desired temperature for a considerable length of time. This has been accomplished by means of a water bath¹ shown in the accompanying figures which was devised and constructed for this purpose. This bath is regulated automatically so that it can be kept at any temperature up to 100° C. as long as desired without variation of more than one- or two tenths of a degree, the change during the alkylation periods being only $0^{\circ}.01$ – $0^{\circ}.02$.

The bath consists of a tank made of 1.25-inch boards lined with tinned sheet copper, the tinned surface being in contact with the water. This tank is 15 inches deep, 15 wide, and 18 long, and holds, when filled to the usual point, about 45 liters. The cover has the lower side made of tinned copper and fits so neatly that very little steam escapes at 95° . The boards of which any such bath is made should be well oiled before use in order to avoid warping, which is otherwise certain to take place. This tank is surrounded by a layer of cow-hair felt two inches thick and the whole is encased in light boards. This packing insulates the bath so well that at about 90° , if kept closed, it does not cool at a rate of more than 2° per hour.

The bath is heated by means of steam pipes running near the bottom, as shown in Figs. I. and II. These pipes are

¹ Mr. E. P. Doetsch and Acree have recently developed a bath similar to the one described below, which has a compartment at one end to hold ice. The outside wheel is connected to a shaft running through the side of the bath close to the top; on this shaft is a small brass cog wheel which turns a larger brass cog wheel on the main central shaft. The bath is heated by a flame underneath when higher temperatures are needed. This bath, which will be described in detail later, is much more efficient than the one described here.

of lead, and have thin walls and an internal diameter of one-half inch. The point at which the steam enters (at *a*, Fig. I or II) is one inch higher than that (*b*) at which the water runs out, and the condenser (*c*, Fig. I) slopes as well, so that there is no chance for water to collect at any place in the system. The inner tube of the condenser runs to the bottom of the steam generator (*e*, Fig. I), so that there is very little loss of water. The small loss which takes place is compensated

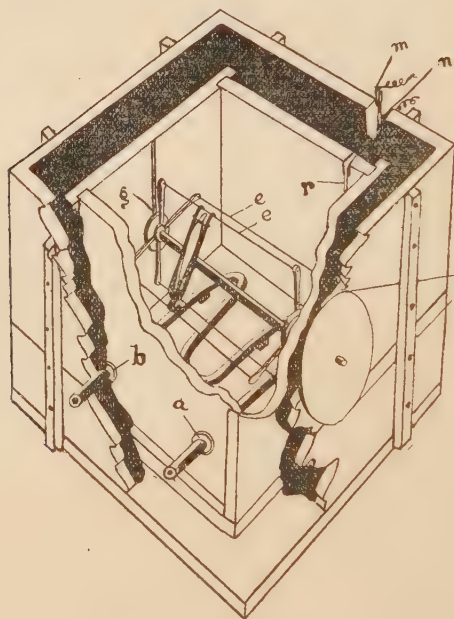


Fig. II.

by the addition of about 300 cc. a week through a tube at (*d*), Fig. I. A glass water-gauge (not seen in Fig. I) shows the level of the water in the steam generator. A small detachable asbestos house, shown in Fig. I, is built around the steam generator to protect it and the flame. All parts of the condenser, as well as the steam supply tube, are made of lead to avoid any chance of breakage when left running overnight, and are protected against radiation of heat when necessary.

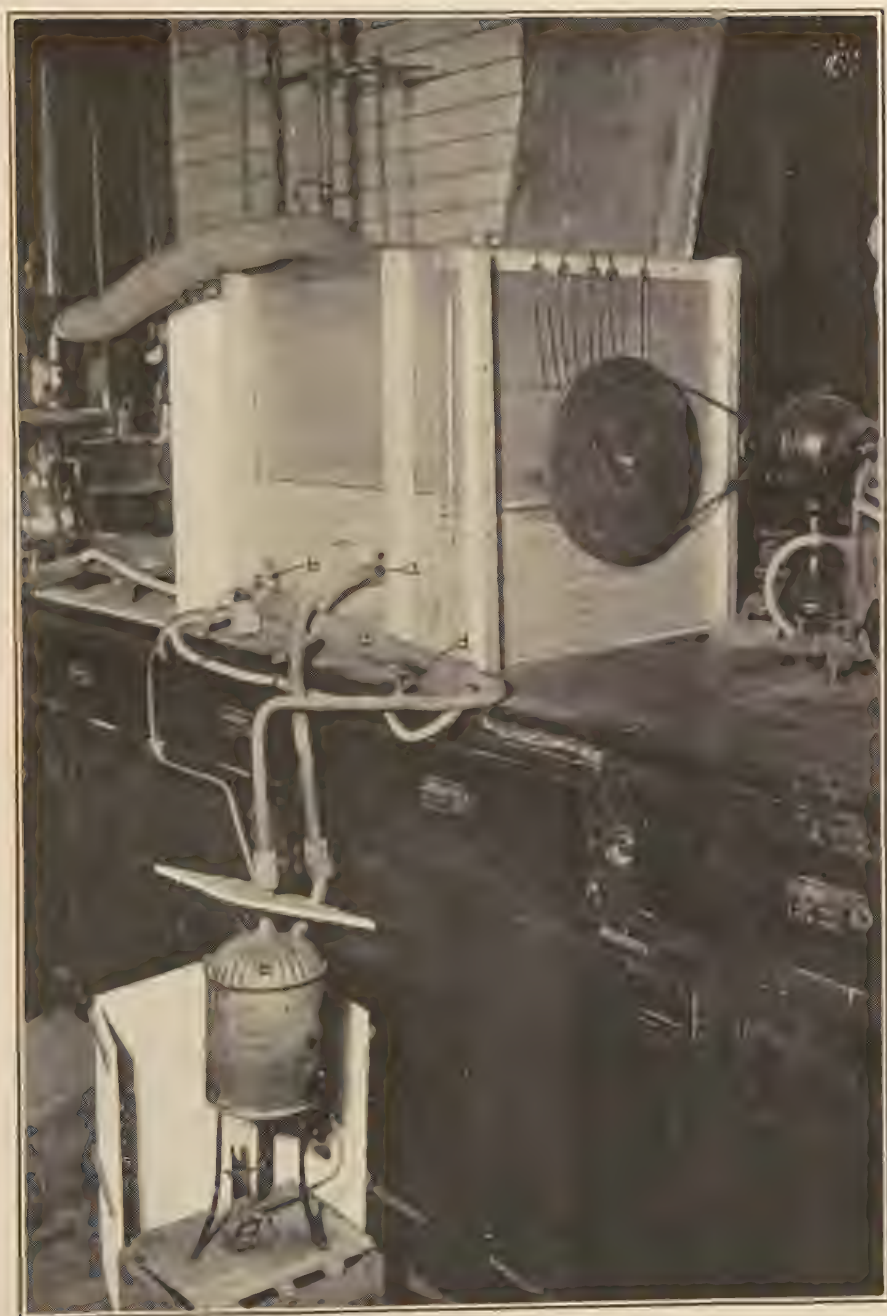


Fig. I.

The tubes running through the walls of the bath have shoulders on the inside, which are fitted with washers and drawn tightly against the side of the tank by collars which screw onto the outer ends. The lead steam pipes are then connected on the inside and outside by means of couplings.

Running through the box is a half-inch brass shaft mounted on bearings as shown in Fig. III. At (c) is a small stuffing box

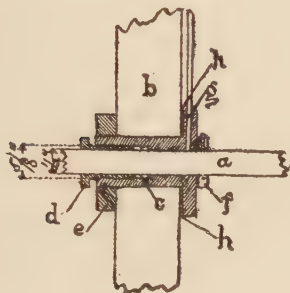


Fig. III.



Fig. IV.

filled with waxed cotton fiber, which is wound round the shaft (a) and jammed in tightly by means of the nut (d) so that the bearing is completely water tight. The shoulder on the inside of the bath is held against a rubber-composition washer (h) by means of the collar (c). The bearing is bored and threaded at (g) and a brass tube introduced, which serves as an oil cup. An oil groove is of course cut on the inside of the bearing.

The shaft carries a framework shown in Fig. II, made completely of brass. The rods (e) are one-eighth inch in diameter and the distance between the diagonally opposite rods is 10 inches. The tubes containing the reagents are attached by fine copper wire to small brass frames similar to that shown in Fig. IV. The sheet brass at (s) furnishes a spring which holds this frame to the brass rods as shown in Fig. II. These frames can be quickly introduced into or removed from the

bath by means of two stout wire hooks. The volume of water is so great that the introduction of a considerable number of tubes at one time does not lower the temperature by a hundredth of a degree. The shaft is kept turning at a rate of 75 to 100 revolutions per minute and both the water and the contents of the tubes are thus kept thoroughly stirred. Flasks or other vessels could be attached to the framework on the shaft without great difficulty.

At first I used at (*r*), Fig. II, a mercury regulator, shaped like that of Reichert except for two bends which allow it to pass out through a slit in the side of the bath. At the binding post (*m*) and the side arm (*n*) electrical connections are made. I have recently, however, discarded this in favor of another form of the Reichert regulator which fits in a hole in a part of the lid which permanently covers the back part of the bath. In this section of the cover there are also two holes for the thermometer. When the mercury touches the point of a platinum wire fastened to one post (*m*), the current passes through a gas regulator of the type devised by Acree, which diminishes the gas supply of the burner under the steam generator, so that the water in the can falls just below the boiling point. When the temperature of the bath again falls, the gas is turned on and in a short time steam is again passing through the pipes. The temperature has been read ordinarily to $0^{\circ}.01$ with a thermometer graduated to tenths of a degree; and readings taken at intervals over several days, when the bath is not in use and not regulated, have in most cases not varied by more than $0^{\circ}.1$.

Analytical Method.

In studying quantitatively the rate and products of the alkylation of the salts of 1-phenyl-4-methylurazole, the greatest difficulty was in finding a method of analysis which could be relied upon to give accurate results. It seems desirable to mention some of the difficulties met with, in order that other workers may avoid errors if any changes in the method are necessary.

It was at first thought that a solution of the salt in water

with ethyl iodide, and sufficient alcohol to bring the latter into solution, could be heated in a sealed tube, then analyzed at once by titration of the unalkylated salt present with standard acid and methyl orange. But, although the pure salt requires nearly the theoretical amount of acid, in the presence of the products from the alkylation experiment no definite end point can be obtained, and in some cases compounds seem to be present which decolorize any of the indicators at once.

The next plan was to evaporate the solution to dryness, add water and excess of alkali, and extract with chloroform. But after a few inaccurate results had been obtained it was found that, although an alcoholic solution of the di-*N*-alkyl derivative can sometimes be evaporated without loss, yet at the temperature of the water bath this substance is appreciably volatile, so that evaporation of a water-alcohol solution is not safe.

It was found, however, that in a solution of 3 cc. water and 2 cc. alcohol the reacting substances would dissolve completely at 60°, and, on washing the tube with 1 cc. more of alcohol and diluting to 50–60 cc. with water, the small amount of alcohol then present would not interfere, as shown quantitatively below, with the complete extraction of the alkylated product. It is also shown below that a chloroform solution of the di-*N*-alkyl product can be evaporated without loss of material.

The hydrolysis of the *O*-alkyl product which is present offered more difficulties. This operation was carried out in an open dish until the volatility of one of the substances was discovered. It was then tried in a closed tube with 3–4 cc. concentrated aqueous hydrochloric acid; but the addition of alcohol up to 50 per cent. failed to bring the substances into solution sufficiently to make the reaction complete in four hours at 90°. By using a *saturated* alcoholic solution of hydrochloric acid, however, the hydrolysis could be accomplished in one hour at 90°. If this heating is continued for six or seven hours, some decomposition other than the hydrolysis

appears to take place, giving products insoluble in alkali. Quantitative data on these points are given below.

The method finally adopted is as follows:

Silver Salt.—An amount of the salt equivalent to 15 cc. 0.1 N solution is weighed into a soft glass tube of about 0.5 inch internal diameter, already drawn out at one end to a capillary and sealed. The other end is then drawn out to a long wide capillary so that the capacity of the tube will not exceed the volume of solution to be used by more than one cc. With this precaution the amount of ethyl iodide volatilized into the free space will be less than one per cent. of the amount present and will, therefore, not appreciably affect the results. The solvents desired—water, alcohol, ether—one of them containing in a known volume the desired amount of ethyl iodide, are then introduced from a burette having a long fine capillary attached to its tip. The tube is then sealed and heated. After cooling, the tips of the capillaries are broken off and the contents of the tube and tips washed into a small Soxhlet extraction apparatus with 1–2 cc. alcohol in small portions, and the silver compounds are extracted with ether on the water bath for half an hour. The ether solution is evaporated, the residue transferred to a separating funnel with the help of chloroform, 50–60 cc. water and a slight excess of alkali (phenolphthalein) added, and this solution is extracted four times with 2–3 cc. chloroform. This is evaporated in a weighed porcelain dish and the weight of total alkylated product thus determined. In order to prevent creeping of the chloroform solution during evaporation, it is necessary to keep a gentle current of air, from the breath or by means of bellows, moving across the dish. The dish is removed from the bath just after the chloroform is apparently all driven off, but does not come to constant weight in a vacuum desiccator for five or ten hours, probably on account of traces of chloroform retained. The loss (of chloroform) during this time may be 5–10 milligrams. On cooling, the substance solidifies or can be made to do so by rubbing.

After being weighed it is transferred to a tube closed at one end, the last traces being washed in by 1–2 cc. alcohol, the

tube is drawn out at the other end, 4 cc. alcoholic hydrochloric acid introduced, and the tube is closed and heated for one hour at 90°. It is then cooled and opened, washed with a little alcohol and this¹ solution warmed to 30°–40° in a vacuum desiccator for a short time in order to remove as much of the hydrochloric acid as possible and part of the alcohol. It is then diluted to 50–60 cc. with water, made alkaline, and extracted again with chloroform. Here, as in every case where the solution contains alcohol, each portion of the chloroform used for extraction is run into a second funnel and shaken up with 40–50 cc. of alkaline water to remove any alcohol it may have dissolved. It is then evaporated again in a weighed dish. The residue should consist of the di-*N*-alkylated product. These residues from one series of experiments are united and identified.

Potassium Salt.—As this is soluble in water, the tube to be used is drawn out at both ends at the outset and the salt introduced in a standard aqueous solution. After being heated and cooled, the tube is emptied as above. Only 2 cc. alcohol are used in each tube and 1–2 cc. are sufficient for washing out the solution, so that, after addition of 50–60 cc. water, the alkylated product can at once be extracted by chloroform, with the precautions mentioned above. From this point the procedure is the same as in the case of the silver salt.

Volatility of 1-Phenyl-2-ethyl-4-methylurazole.—The data given below show the loss of the di-*N*-alkyl derivative produced by evaporation with alcohol and aqueous hydrochloric acid, and also by simple heating on the water bath. The first three evaporations with acid were more than sufficient to decompose all of the 3-ethoxy compound present, so subsequent losses must be due to the volatility of the compound in question. The weight given is that of the mixture of di-*N*-alkyl product and 4-methyl derivative remaining in the dish after the evaporation.

- I. 0.122 gram = weight after three evaporations.
- 0.1075 gram = weight after one more evaporation.
- 0.095 gram = weight after one more evaporation.

¹ This procedure is no longer used, the solution being diluted at once with water.

- II. 0.186 gram = weight after three evaporations.
 0.1105 gram = weight after one more evaporation.
 0.1065 gram = weight after heating 15 minutes longer.
 0.0970 gram = weight after heating 30 minutes longer.

Evaporation of the chloroform solutions is safe: 0.313 gram substance was dissolved in chloroform and the solution evaporated. The residue weighed 0.310 gram, the loss being 1 per cent. Experiments below give further evidence on this point.

The completeness of hydrolysis of the 3-ethoxy compound in an open dish and the nonvolatility of the 1-phenyl-4-methylurazole are shown by the following experiment: 0.100 gram 1-phenyl-3-ethoxy-4-methylurazole was dissolved in alcohol and evaporated to dryness with addition of aqueous hydrochloric acid three times. The weights of the residues after the successive operations were 0.0855, 0.0855, 0.0855 gram, respectively. The calculated weight was 0.0870 gram, the error being 1.5 per cent.

Extraction of Alkylated Products from Alcohol-Water Solution.—To 1-phenyl-3-ethoxy-4-methylurazole (0.0855 gram) and 1-phenyl-2-ethyl-4-methylurazole (0.0915 gram) were added 60 cc. water and 4 cc. alcohol. The solution was extracted with four portions of chloroform of 2-3 cc. each. After being shaken up with water these were evaporated in a weighed porcelain dish. The weight of the residue was 0.177 gram instead of 0.180 gram, the amount taken at the start.

In another case a solution from which 0.155 gram material had been obtained by four extractions was extracted a fifth time and this last portion of chloroform was evaporated in a separate dish. The substance obtained weighed only 0.0005 gram, showing that the four extractions were sufficient. The solutions were generally extracted four or five times.

Hydrolysis of 1-Phenyl-3-ethoxy-4-methylurazole.—A portion of the compound, weighing 0.199 gram, was heated in a sealed tube with 4 cc. N aqueous hydrochloric acid for 3.5 hours at 91°. All of the substance was recovered (0.201 gram).

A mixture of 3 cc. alcohol and 3 cc. concentrated aqueous acid gave no satisfactory results.

The hydrolysis was found to be complete after heating the material with 4 cc. concentrated alcoholic hydrochloric acid for one hour at 90°. The solution was then made alkaline and any dialkyl body present extracted with chloroform.

I. 0.135 gram ethoxy body was heated with 4 cc. acid. Extraction with chloroform gave a residue of 0.001 gram.

II. 0.1085 gram substance was heated with 4 cc. acid diluted with 1 cc. alcohol. The residue weighed 0.0015 gram.

III. 0.0855 gram ethoxy body and 0.040 gram 2-*N*-ethyl derivative were heated together with 4 cc. acid. 0.042 gram dialkyl derivative was recovered.

IV. 0.104 gram ethoxy body and 0.149 gram 2-*N*-ethyl body were heated with 4 cc. acid diluted with 1 cc. alcohol. 0.1505 gram dialkyl derivative was recovered.

In experiments III and IV, the alkaline solutions, after extraction, were acidified and the precipitate filtered, washed, and dried. It was identified as 1-phenyl-4-methylurazole, melting at 223°.

An attempt was made to determine the amount of *O*-alkyl derivative present in a mixture by hydrolyzing it with gaseous hydrochloric acid and measuring the volume of ethyl chloride formed, but the experiments were not carried far enough to give results that were of any value. The Zeisel method should work beautifully in all these cases, but does not seem to have a great advantage over the above method either in accuracy or convenience. I shall compare these two methods very accurately.

Decomposition of 1-Phenyl-2-ethyl-4-methylurazole by Alkali.
—The di-*N*-alkyl compound (0.265 gram) was dissolved in 4 cc. alcohol, 5 cc. 2 *N* aqueous alkali were added, and the solution was allowed to stand 49 hours. Extraction with chloroform then gave back only 0.0945 gram material. A weakly acid solution can, however, apparently stand several days or longer without decomposition.

In another case about 0.225 gram di-*N*-alkyl derivative, which had been allowed to stand two days with alkali, gave on extraction only 0.1665 gram substance—a loss of 0.060

gram. The mother solution was acidified and again extracted several times, but only 0.022 gram substance was obtained. If the decomposition by alkali were simply a breaking open of the ring between positions 4 and 5, the compound obtained should be soluble in alkali, but precipitated by acids. From the above figures it seems that the decomposition goes further than that.

In general, the analytical method seems to be accurate to about 5 per cent. and this communication is to be judged only from this light. Future work will perhaps enable us to get closer results.

Alkylation Experiments.

1. Among the first experiments, which were carried out before all of the sources of error mentioned above were known and which were therefore rendered inaccurate, a few are interesting as showing roughly the relative rates of alkylation in benzene and alcohol. These experiments were not carried out according to the general method described above. The sodium and silver salts of 1-phenyl-4-methylurazole were used, and the solvent was 12 cc. of either dry alcohol or benzene. The contents of the tubes were evaporated to dryness in open dishes, but, as stated above, the loss probably was not great and would be approximately the same for the two solvents. The column headed "per cent. reacted" gives the percentage of original salt converted into alkylated product. This is easily calculated from the fact that 0.3288 gram would have been the weight of product in each case if the reaction had been complete. The figures for the relative amounts of *O*- and *N*-alkylated products are of no value and are omitted. One molecule of ethyl iodide was used in every case.

The potassium salt probably failed to react in benzene on account of its insolubility. The silver salt, however, reacted at 22° three times, and at 51° over four times as fast in benzene as in alcohol. If the difference is due to solubility it must be very great, since the reaction appears to be largely ionic, as shown below, and the alcohol is, of course, the much more strongly ionizing solvent of the two.

Salt used.	Wt. of salt.	Solvent.	Temp.	Time in in hrs.	Wt. prod.	Per cent. reacted.
K	0.344	Benzene	22°	336	0.001	
K	0.344	Benzene	22°	360	0.001	
K	0.344	Alcohol	51°	93	0.186	56.6
K	0.344	Benzene	51°	96	0.0025	
Ag	0.447	Alcohol	22°	240	0.074	22.5
Ag	0.447	Alcohol	22°	241	0.076	23.1
Ag	0.447	Benzene	22°	336	0.1835	55.8
Ag	0.447	Benzene	22°	336	0.1945	59.1
Ag	0.447	Alcohol	51°	93	0.059	18.0
Ag	0.447	Alcohol	51°	93	0.0675	20.5
Ag	0.447	Benzene	51°	96	0.313	95.2
Ag	0.447	Benzene	51°	96	0.304	92.5

2. Alkylation of Potassium 1-Phenyl-4-methylurazole.

All of the experiments below were carried out according to the process described under "Analytical Method."

Standard Solution of Potassium 1-Phenyl-4-methylurazole.—The free urazole derivative (4.779 grams) was neutralized with N potassium hydroxide, 25.04 cc. being required instead of 25.00 cc. calculated, and this solution was diluted to 50 cc. Three cc. then contained 0.344 gram salt and were equal to 15 cc. 0.1 N solution.

Standard Alcoholic Solution of Ethyl Iodide.—Into a 100 cc. flask half filled with absolute alcohol 11.75 grams ethyl iodide were weighed, and the solution was then diluted to the mark and 0.43 cc. more alcohol added. One hundred cc. of solution then contained 11.70 grams ethyl iodide, or 2 cc. contained 0.234 gram and were equivalent to 15 cc. 0.1 N solution. In the experiments described below, each tube contained 3 cc. of the potassium urazole solution and 2 cc. of the ethyl iodide solution.¹ The hydrolysis was carried out in each case by heating one hour at 90° with 4 cc. concentrated alcoholic hydrochloric acid, diluted by 1-2 cc. used in transferring the substances to the tubes.

In the table below, Column III gives the total weight of alkylated product obtained from the chloroform solution

¹ In the recent work a special piece of apparatus, made by Mr. H. C. Robertson, has been used for measuring and transferring the alcoholic solutions without appreciable volatilization of alkyl halide.

used for extraction. If the reaction had been complete this should have been in each case 0.329 gram. After the alkaline solution had been extracted with chloroform the free alkali was neutralized with 0.0989 N sulphuric acid, phenolphthalein being used as indicator. Methyl orange was then added and the unchanged potassium urazole salt present titrated with the same acid. The amount required, measured in cc., is given under V. Since the salt introduced into the tube was equivalent to 15 cc. 0.1 N solution, the part still unalkylated is easily calculated and that value (in per cent.) is given under VI. The sum of the values in IV and VI should obviously be 100.0, but, as stated above, the end point of the titration is not sharp, so that where there is a discrepancy the value in column IV is usually more reliable. Column VII shows what percentage of the total alkylated product contained the entering radical attached to nitrogen:

Table I.—Potassium Salt at 60°.

I. No.	II. Time.	III. Total prod.	IV. Per cent. reacted.	V. Acid to titrate.	VI. Per cent. not reacted.	VII. Wt. N-ester.	VIII. Per cent. N-ester.
1	30 m.	0.060	18.3	12.70	84.7	0.0585	(97.5)
2	30 m.	0.063	19.2	12.62	84.1		
3	30 m.	0.0545	16.6	12.00	80.0	0.0490	89.9
4	1 h.	0.079	24.0	11.12	74.1	0.075	95.0
5	1 h.	0.1045	31.8	10.37	69.1	0.0935	89.5
6	1 h.	0.095	28.9	10.77	71.8	0.0845	89.0
7	2 h.	0.158	48.05	7.95	53.0	0.144	91.1
8	2 h.	0.159	48.35	8.17	54.5	0.146	91.8
9	4 h.	0.207	63.0	5.85	39.0	0.1815	87.7
10	4 h.	0.206	62.7	5.86	39.1	0.1865	90.5
11	24 h.	0.273	83.0	2.46	16.4	0.2455	89.9

Mean per cent. N-ester about 91.0

The various lots of 1-phenyl-2-ethyl-4-methylurazole obtained in these experiments were united and analyzed without further purification.

Analysis:

0.1405 gram substance gave 23.6 cc. nitrogen at 20°.4 and 753 mm.

	Calculated for $C_{11}H_{13}O_2N_3$.	Found.
N	19.22	19.43

This substance was purified as described on p. 533, and in the following alkylations the 2-4-di-*N*-alkyl derivative was identified by its melting point.

In the following table the averages of values from Table I have been substituted in the equation for the velocity of a bi-molecular reaction, $\frac{dx}{dt} = K(A-x)^2$, (the initial concentrations, A , of the two substances being the same), which on integration becomes $1/t \frac{x}{A-x} = A K$; A and x are given in gram molecules, the time, t , in hours.

Table II.

I. Time.	II. Per cent. reacted.	III. $A \times 10^4$.	IV. $x \times 10^4$.	V. $(A-x) \times 10^4$.	VI. $A K$.
0.5	18.0	15	2.70	12.30	0.439
1.0	30.35	15	4.19	10.81	0.453
2.0	48.2	15	7.23	7.77	0.465
4.0	62.85	15	9.43	5.57	0.423

In the one-hour values that from experiment No. 4 is omitted as it is so much lower than the rest. The sum of the values in columns IV and VI (Table I) would indicate that the analysis of the contents of that tube was correct, so that an error was perhaps made in filling the tube. If this value is averaged in with the others, the value of $A K$ is 0.393. If the highest figures for the first two time periods are used, the values for $A K$ become 0.461 and 0.466, respectively. The experiment continued for 24 hours is of no value in this connection since the ethyl iodide not used for alkylation was decomposed long before the end of that time.

Two tubes were filled and simply kept at room temperature, which averaged about 22°. The ethyl iodide did not completely dissolve at this temperature, but the tubes were shaken frequently. The quantities of reagents and solvents were the same as in the experiment at 60°.

Table III.—Potassium Salt at 22°.

I. No.	II. Time.	III. Total product.	IV. Per cent. reacted.	V. Acid to ti- trate.	VI. Per cent. not reacted.	VII. Wt. <i>N</i> -ester.	VIII. Per cent. <i>N</i> -ester.
12	312 h.	0.1665	50.6	7.5	50.0	0.1555	93.4
13	312 h.	0.1665	50.6	7.5	50.0	0.1600	96.1
Mean per cent. <i>N</i> -ester = 94.8							
Melting point of <i>N</i> -ester = 50°-51°							

Table IV.—Potassium Salt at 90°.

I. No.	II. Time.	III. Total prod.	IV. Per cent. reacted.	V. Acid to titrate.	VI. Per cent. not reacted.	VII. Wt. <i>N</i> -ester.	VIII. Per cent. <i>N</i> -ester.
14	4 $\frac{1}{3}$ m.	0.0725	22.1	11.25	75.0	0.064	88.3
15	30 m.	0.1945	59.1	4.28	28.5	0.178	91.5
16	15 h.	0.262	79.7			0.234	89.3
Mean per cent. <i>N</i> -ester = 89.7							
Melting point of <i>N</i> -ester = 50°-50°.5							

The relative amounts of *N*- and *O*-ethyl derivatives found are thus nearly or quite independent of the temperature, although there seems to be a decrease in the per cent. of *N*-ester as the temperature rises, which will be investigated very closely. Since so few experiments were carried out at 22° and 90°, the results hardly justify the conclusion that there is an appreciable change in the ratio.

3. Alkylation of Silver 1-Phenyl-4-methylurazole.

In the alkylation of the silver salts, since a large amount of solvent must be used for extracting the insoluble residue, ether was used in place of alcohol or water. This also prevented decomposition of the ethyl iodide to any such extent as took place with the other solvents. Each tube contained a weight of silver salt (0.447 gram) equivalent to 15 cc. 0.1 *N* solution.

Standard Ether Solution of Ethyl Iodide.—A 50 cc. flask was partly filled with ether, weighed, and 3.918 grams ethyl iodide added. The solution was diluted to the mark and 0.22 cc. more ether added. Six cc. of this solution then contained 0.468 gram ethyl iodide, or two molecules for every one of silver salt. Column IV gives the per cent. of *salt* which had reacted in the given time.

Table V.—Silver Salt at 60°.

I. No.	II. Time.	III. Total prod.	IV. Per cent. reacted.	V. Wt. N-ester.	VI. Per cent. N-ester.
17	45 m.	0.0505	15.4	0.0215	42.6
18	45 m.	0.0515	15.7		
19	125 m.	0.212	64.5	0.0840	39.6
20	125 m.	0.206	62.6	0.0730	35.4
21	23.5 h.	0.313	95.2	0.117	37.4
22	23.5 h.	0.291	88.5	0.106	36.4
23	96.5 h.	0.300	91.2	0.1125	37.5
24	96.5 h.	0.307	93.4	0.1085	35.4

Mean per cent. N-ester = 37.8
 Melting point of N-ester = 48°-49°

Table VI.—Silver Salt at 90°.

I. No.	II. Time.	III. Total prod.	IV. Per cent. reacted.	V. Wt. N-ester.	VI. Per cent. N-ester.
25	8 m.	0.0800	24.3	0.025	31.3
26	8 m.	0.0855	26.0	0.027	31.6
27	90 m.	0.2985	90.7	0.109	36.5
28	90 m.	0.3165	96.3	0.1105	34.9

Mean per cent. N-ester = 33.6

Experiments with the silver salt at 25° will be carried out in the future. The percentage of *N*-alkylated product formed at the two temperatures does not vary greatly here, although there is apparently a slight decrease in the per cent. of *N*-ester with rise in temperature.

Rearrangement Experiments.

The result of these experiments has been to show that 1-phenyl-3-ethoxy-4-methylurazole is not rearranged appreciably into the isomeric 2-*N*-ethyl derivative under the influence of ethyl iodide at the temperatures at which the above alkylations were carried out, nor does rearrangement take place at higher temperatures as far as tried.

Two tubes were filled with 0.200 gram 1-phenyl-3-ethoxy-4-methylurazole, 2 cc. alcohol, 3 cc. water, and 0.213 gram (1.5 mols.) ethyl iodide, and heated at 90° for 24 hours. They were then opened and the contents treated as in the case of the alkylation of a potassium salt. After hydrolysis the substance insoluble in alkali from each tube weighed 0.002 gram.

A tube similarly filled, except that it contained 9.5 molecules of ethyl iodide, was heated 2 hours at 150°. From this 0.004 gram product insoluble in alkali was obtained.

A last tube, which contained 0.200 gram material, 2 cc. benzene and 0.143 gram (1 mol.) ethyl iodide, was heated an hour at 200°, then an hour at 160°. From this 0.002 gram product insoluble in alkali was obtained.

This small amount of substance did not in any case look like the 2-*N*-ethyl derivative nor did it have the characteristic odor of that substance. It was probably the result of slight decomposition or else was present as impurity at the outset. The ethoxy compound used was not in perfectly pure condition.

The experiments above on the hydrolysis of the ethoxy derivative are also of interest in this connection. A mixture of the 2-*N*-ethyl and 3-ethoxy compounds was heated with alcoholic hydrochloric acid. The results show that neither hydrochloric acid nor the ethyl chloride (formed during the reaction) effects a rearrangement of either compound into the other.

Hydrolysis of Ethyl Iodide.—Potassium phenylurazole and the salt of the 4-methyl derivative undergo some hydrolysis. The potassium hydroxide so formed would decompose ethyl iodide, and water to a less extent produces the same effect. Some action of this sort evidently took place in the alkylation experiments above since the yield of alkylated products stopped increasing after a certain time, although the reaction was not complete. It was desired to make an approximate study of the correction for this decomposition in the reaction above and the plan was to try the action on ethyl iodide of some salt hydrolyzed to about the same extent as the urazole salt used. The compound that I chose for this purpose was potassium carbonate in 0.05 N solution.¹

As seen, the errors of analysis above are so great that such a correction is not of great value, but the figures for the experiments with the carbonate are of interest.

A standard solution of potassium carbonate was made by

¹ Am. Chem. J., **29**, 453 (1903).

dissolving 6.92 grams of the salt in water and diluting to 200 cc. Two cc. of solution then contained 0.0692 gram, equivalent to 5 cc. tenth-molecular normal solution, or to 10 cc. of the acid solution called 0.1 N above—that is, one-third of the molecular concentration of the potassium urazole used above. Two cc. of this solution neutralized 9.95, 10.01, 10.03 cc. standard sulphuric acid (methyl orange). The mean is 10.00 cc. Two cc. of the alcoholic ethyl iodide solution of the usual strength were employed.

Each tube contained 0.234 gram ethyl iodide and 0.0692 gram carbonate.

The equation for the reaction velocity is

$$\frac{dx}{dt} = K(A - x)(B - x),$$

and on integration, when $x = 0$ if $t = 0$,

$$1/t \log \frac{B(A - x)}{A(B - x)} = (A - B)K \text{ or } 1/t \ln \frac{B(A - x)}{A(B - x)} =$$

$$0.4343 (A - B)K = (A - B)K'.$$

Let B be the initial concentration of ethyl iodide and A that of potassium atoms. The molecular concentration of potassium carbonate is 5×10^{-4} , but since each molecule of ethyl iodide decomposed into hydriodic acid neutralizes only half a molecule of carbonate, it is better to define A as above, so that x will have the same relation to A and B .

The temperature was 60° and the times taken were the same as in the alkylation of the potassium salt above at that temperature. The time is measured in hours. The titration is given in cc.

Table VII.

$A \times 10^4$.	$B \times 10^4$.	Time.	Titration.	Mean titration.	$x \times 10^4$.	$(A - B)K'$.
10	15	0.5	9.23	9.21	0.79	0.0562
10	15	0.5	9.19			
10	15	1.0	8.54	8.58	1.42	0.0537
10	15	1.0	8.61			
10	15	2.0	7.49	7.49	2.51	0.0543
10	15	2.0	7.48			
10	15	4.0	5.96	5.95	4.05	0.0511
10	15	4.0	5.94			

The above results leave no doubt as to the order of the reaction, but in the present case that indicates nothing as to the mechanism.¹

A solution of alcohol and water also decomposes ethyl iodide, as shown below. Tubes were filled with 2 cc. alcohol containing 0.234 gram ethyl iodide and 3 cc. water. If the ethyl iodide were all converted into hydriodic acid it would neutralize 15 cc. 0.1 N alkali. The amount of acid present after different intervals was determined by titration.

If the reaction were not reversible, the velocity should apparently depend only on the concentration of the ethyl iodide, since the concentration of the alcohol is about 435×10^{-4} and that of the water 1670×10^{-4} , and the change in either of them is, therefore, inappreciable. The chance of error in the first titrations is of course great. The great variation in the value of K is most probably due to the reversibility of the reaction. Others in this laboratory have since obtained a great deal of evidence for this.

The equations are,

$$\frac{dx}{dt} = K(A - x)$$

$$1/t \log \frac{A}{A - x} = K \text{ or } 1/t \ln \frac{A}{A - x} = 0.4343 K = K'.$$

The experiments were carried out at 60°. The times are given in minutes.

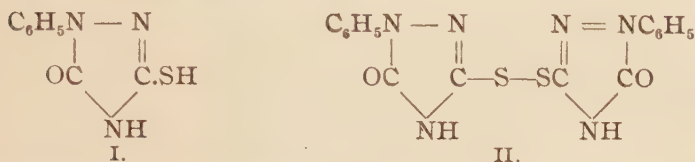
Table VIII.

Time.	Titration.	$A \times 10^4$.	$x \times 10^4$.	$K' \times 10^3$.
31	0.34	15		
31	0.34	15	0.32	0.30
60	0.38	15		
60	0.42	15	0.40	0.20
120	0.74	15		
120	0.71	15	0.73	0.18
243	1.20	15		
243	1.21	15	1.21	0.15

Alkylation of Potassium 1-Phenyl-3-thiourazole.—A few ex-

¹ This reaction and that of alkyl halides with alkalis, with phenolates and alcoholates in absolute alcohol, and with urazole salts are being investigated.

periments have been carried out on the action of ethyl iodide on the potassium salt of 1-phenyl-3-thiourazole,¹ formula (I):



This salt reacts with ethyl iodide in the cold, giving the 3-ethylthio derivative. The thiol group at 3 is so much more strongly acid than the enol group of the oxygen compounds that the metal in the monopotassium salt is probably practically all at 3. Although, from the conclusion reached above, we should expect a small amount of *N*-salt to be present also, the amount of *N*-alkyl product formed is so small as to be negligible, the thio ethyl derivative when first isolated being practically pure. I shall later measure the ratio *N*-ester : *S*-ester given by thio-amides. By using this compound we are thus enabled to study the alkylation at practically one position alone and I hope, by further work, to obtain certain evidence on the question as to whether the alkylation reaction is between molecules or ions. The results already obtained by myself and recently by Dr. F. M. Rogers indicate that both the molecules and the ions are concerned in the reaction.

The course of the reaction is easily followed by titration of the reaction mixture with standard iodine solution, which converts the unchanged salt into a disulphide, formula (II), with formation of potassium iodide. A 0.1 N solution of potassium phenylthiourazole was prepared and 5 cc. were titrated with iodine solution. The results are given in Column II of the following table. Five cc. portions were then mixed with equal volumes of ethyl iodide solution of the same concentration. The solvent in each case was 50 per cent. alcohol. These mixed solutions were allowed to stand at 25° for various lengths of time and titrated. The results of the titration, giving the amounts of unchanged salt, are found in

¹ Acree: Ber. d. chem. Ges., **36**, 3151 (1903).

Column III. We now have values which can be substituted in the equation for a second order reaction,

$1/t \frac{x}{A-x} = A K$, and the values obtained for $A K$ and K are given in Columns V and VI:

Table IX.

<i>t.</i>	<i>A.</i>	<i>A-x.</i>	<i>x.</i>	<i>A K.</i>	<i>K.</i>
10	8.55	6.66	1.89	0.028	0.0033
30	8.55	4.55	4.00	0.029	0.0034
61	8.55	3.22	5.33	0.027	0.0032
120	8.55	1.97	6.58	0.029	0.0034
193	8.55	1.38	7.17	0.029	0.0034
10	9.90	7.51	2.39	0.032	0.0032
13	9.90	6.92	2.98	0.033	0.0033
21	9.90	6.00	3.90	0.031	0.0031
30	9.90	5.13	4.77	0.031	0.0031

In the second series, as is easily seen, a slightly more concentrated solution of urazole salt was used.

Conclusions.

In the above paper evidence has been presented which bears on the general question of tautomerism. The ground has been taken that the great similarity in the behavior of different tautomeric substances and their salts makes it probable that all of the phenomena commonly included under the term tautomerism arise from the same cause. The possible explanations of these phenomena have been discussed and the following conclusions reached:

1. The assumption of different structures for the potassium and silver salts of any tautomeric compound is of no assistance in explaining the reactions of our urazoles, because on careful study both salts are found to behave essentially alike in that mixtures of *N*-ester and *O*-ester are obtained from both.

2. The theory that when a salt gives two isomeric derivatives on alkylation one is an intermediate product in the formation of the other cannot hold in the present case, because (1) neither derivative has been found to rearrange appreciably into

the other, and (2) the ratio of the two products is practically the same at all times during the course of the reaction.

3. It is shown that the "addition theory" does not explain as easily as the theory here advocated the nature of the reaction, and the fact that in a large number of reactions the velocity *decreases* upon the addition of many electrolytes, whereas an *increase* is required by the "addition theory."

4. It is shown that *the assumption of two different salts in equilibrium* will account for all the facts known in connection with our compounds.

5. The salts of phenylurazole were treated with alkyl halides and found to yield in all cases a mixture of *N*-ester and *O*-ester.

BIOGRAPHY.

The author of this dissertation, Roger Frederic Brunel, was born in Portland, Maine, on December 21, 1881. His preparatory training was received at the public schools of Portland. In 1899 he entered Colby College and graduated from there in 1903 with the degree of Bachelor of Arts. In October, 1903, he entered the Johns Hopkins University. During the year 1904-'05 he was laboratory assistant to Dr. Gilpin and during the year 1905-'06 held the position of lecture assistant to Prof. Renouf. His subordinate subjects were Physical Chemistry and Physics.

